

THE RHEUMATOID DISEASE FOUNDATION

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July 23, 1984

JOHN R. A. SIMOONS, Ph.D.
President

To: All Board Members and Scientific Advisory Committee
From: John R.A.Simoons, Ph.D.
Subject: Selection of CLOTRIMAZOLE for clinical evaluation

Introduction:

The use of anti-protozoal compounds against rheumatoid disease was introduced in 1975 by Dr. Wyburn-Mason when he postulated his hypothesis of a protozoal causation of these diseases which could be cured by treating the patients with anti-protozoal compounds. The first compound used by Roger was Clotrimazole (The Lancet, Febr. 28, 1976, 489).

My first meeting with Roger was on October 28, 1975 together with Dr. Lukas, medical director of Organon England, at his home in Richmond. We discussed his experiments and the results of the first group of 54 patients which he had successfully treated and cured with Clotrimazole. From my notes of this meeting I quote:

1. I treated patients who had up to 30 years active RA and were on Gold, Corticosteroids, Penicillamine or a combination of these drugs.
2. At the Rheumatoid Arthritis Clinic of the Hounslow Hospital we wanted to reach a dosis of 100mg/Kg of Clotrimazole but most patients could not tolerate this. We had to administer anti-emetic drugs, Kaopectate and Paregoric to stop the diarrhea. We finally arrived at a dose of 20-30mg/Kg per day.
3. In some patients the symptoms of pain and swelling disappeared within three days but it took 2 - 4 weeks for a complete remission of the disease.
4. Most patients developed severe inflammation, pain and swelling shortly after the medication was administered which, however, gradually died down upon continued administration.

We further discussed his isolation of the protozoa by "thermotropism" and he informed us of Bayer's interest to conduct a double-blind trial in England and Germany with Clotrimazole to confirm his findings. He requested that I contact Prof. Bernard Levine of New York University Medical Center, Dr. Robert Bingham and Dr. John Decker of the Arthritic Division of the Bethesda Naval Medical Institute of Washington D.C. who had contacted him and agreed to review his findings.

Roger also gave me the names of four patients from the USA who he treated and cured and requested to contact them for their personal medical history. Before returning to the US, I obtained 200 "Canesten" (Clotrimazole) 0.5 g tablets from a research colleague in Germany, which I used to treat my daughter, Mrs. Mavis Vecchio.

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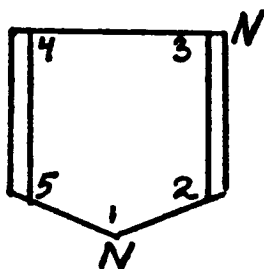
THE RHEUMATOID DISEASE FOUNDATION IS A PROJECT OF
THE ROGER WYBURN-MASON & JACK M. BLOUNT FOUNDATION
FOR THE ERADICATION OF RHEUMATOID DISEASE

TAX EXEMPTION APPROVED BY THE UNITED STATES INTERNAL REVENUE SERVICE
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I visited with Roger at least once a year and often twice until his death in 1983. He gave me a copy of his manuscript "The causation of rheumatoid disease and many human cancers- A New Concept in Medicine" during our second meeting in March 1976.

From the several anti-protozoal compounds used by Roger to treat RA he obtained the best results with the IMIDAZOLE compounds. Roger was not the first to apply an Imidazole compound against RA, because ABD RABBO used BT 985, a derivative of Naxogin and a compound synthesized by Merck A.G. for treating rheumatoid arthritis and lupus erythematosus and obtained "beneficial effects" (Am.J.of Trop.Med.Hyg.1972,75,64). Roger was looking for compounds which were specifically effective against Naegleria Fowleri and asked that I screen several compounds for their "in vitro" activity against these organisms. Together with my colleagues at the Brocades Research Institute in Haarlem, the Netherlands, we reviewed several compounds and tried to determine the relation between the chemical structure and pharmacological activity of these compounds with an Imidazole nucleus.

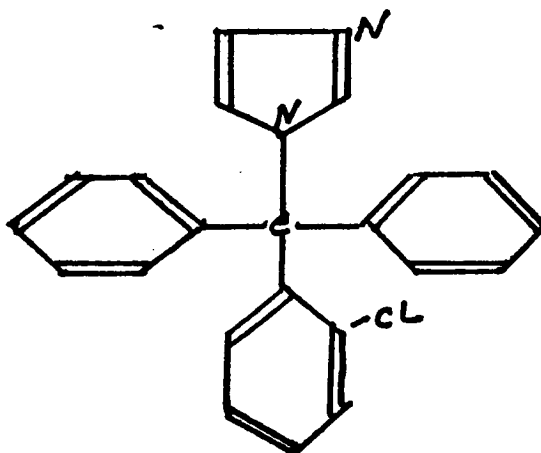
From my report to him of May 11, 1978 I quote the following:



IMIDAZOLE NUCLEUS

1. It appears that the anti-protozoal activity of Imidazole compounds is linked to Imidazole compounds with a substitution at the ONE position of chemical moieties with aliphatic or aromatic structure.
2. The presence of a NITRO group at the 4 or 5 position increases the toxicity and the LD-50 in rats considerably but retains their anti-protozoal activity.
3. Compounds with a substitution at the TWO position such as Mebendazoline are not effective and listed as "pesticides".
4. Compounds with a substitution at the THREE position (Miconazole) are also not effective against Naegleria but listed as active against candidiasis and moniliasis.

5. The most potent Imidazole compound against Naegleria Fowleri "in vitro" is Clotrimazole, followed by Tinidazole, Nimorazole, Ornidazole and Flagyl, in this order. All these compounds are substituted at the ONE position but the only one without a NITRO group is Clotrimazole.



CLOTRIMAZOLE FORMULA

The use of Clotrimazole as an anti-fungal agent and several related compounds for use as antimycotics is disclosed in U.S. Patent # 3,657,445 of April 18, 1972 to Buchel et al. The use of Clotrimazole is also described in the September 12, 1975 issue (volume 17, #19, pages 77-78) of the "Medical Letter".

From the 25 related Imidazole compounds it appeared that N-triphenyl-methyl-imidazolium chloride (Clotrimazole) was most effective "in vitro" against human-pathogenic fungi, Candida Albicans as further disclosed in U.S. Patent # 3,705,172 by Buchtel and assigned to Bayer A.G. of December 5, 1972.

Clotrimazole was suggested for use in humans against dermatomycoses, caused by fungi and organomycoses caused by yeasts and mould fungi. The oral dose is in the range of 20 to 100 mg/Kg for 10 to 60 days.

The LD-50 (Lethal dose in which 50% of the test animals died) for mice, rats, rabbits, dogs and cats, lies between 600 and 1200 mg per Kg body weight in oral administration.

Before Bayer AG could obtain the approval from the British authorities for the safety of Drugs (Previous Dunlop Committee) they had to submit toxicity and other biological data on Clotrimazole of which I obtained a copy. The copy was sent to Dr. Robert Turner for his review. Most of the data are printed in "Postgraduate Medical Journal", July 1974, Suppl. (1) vol. 50 but the so-called "investigator's manual" is more extensive.

The ONLY double-blind study with Clotrimazole was conducted by Dr. Wojtulewski (Annals of the Rheumatic Diseases, 1980, 39, 469-472). Roger and I visited with Dr. Wojtulewski after completion of the study and discussed his results of the study and more important - of the continuation of the open study for 6 to 8 months in his patients. The results were very encouraging but the dose was too high (40mg/Kg first week, followed by 80mg/Kg for seven weeks, daily administration) and resulted in severe adverse effects i.e. nausea, vomiting, diarrhea, anorexia, lethargy, drowsiness, pain on micturation and seven of the 24 patients in the Clotrimazole group withdrew. We know that most of these "adverse effects" are part of the Herxheimer reaction and will always appear.

When preparing for a clinical study in the United States one must bear in mind that the following requirements MUST be met:

- a) A complete DFUG MASTER FILE of the compound to be evaluated must have been filed with the Food and Drug Administration. This must include all chemical, biological, toxicity (acute, subchronic & chronic in at least three animal species) teratogenicity, oncogenicity and clinical pharmacology data. The Drug Master File (DMF) is registered and receives a number but is NOT reviewed by the FDA until one files an IND.
- b) After an IND (Investigational New Drug Application) is filed by the sponsor, the FDA has 30 days to respond and will then review the DMF data. If not complete, the FDA will request further data which may take several years to obtain.
- c) In the case of Clotrimazole we KNOW that the DMF is complete because Bayer obtained IND and NDA's for Clotrimazole as topical application, vaginal tablets and last year for troches for trichomonal and other infections.

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d) After the sponsor completes the clinical evaluation based on the IND and protocol for the study he must prove from the results that:

1) the drug is safe in the dose administered

2) the drug is effective for the condition which is treated. "Effective" means that the drug is as good as or better than the standard drug used to treat that condition. Please note that ALL so-called non-steroidal compounds must be as good as Aspirin or better in order to obtain approval of effectiveness.

The IND evaluation is referred to as Phase TWO study in which the drug is administered to carefully supervised patients suffering from the disease for which the drug is intended.

Phase ONE in which the drug is administered to healthy volunteers to determine toxicity (in humans), metabolism, absorption, elimination, drug/response curve, blood levels etc. must have already determined the safety in humans before an IND will be approved. We know that Bayer already obtained data from the Phase ONE study which were acceptable and would guarantee that our drug protocol of 20mg/Kg will be approved.

After the human pharmacology (Phase ONE) and Clinical evaluation (IND-Phase TWO) are completed, the Pharmaceutical Company will submit a New Drug Application (NDA) which will contain additional data in multicentre studies by approved investigators nationwide in which patients suffering from the disease are treated and carefully monitored. Only after the data has been reviewed by the FDA (within 180 days) and are found to be satisfactory will the FDA approve the NDA.

An approved NDA means that the Company may introduce the drug after labeling, claims, dosage, warnings etc. are approved by the FDA.

Of all the Imidazole compounds available for evaluation only CLOTRIMAZOLE would be accepted for a clinical evaluation based on the availability of the DMF and Phase ONE study.

TINIDAZOLE (Fasigyn) has a DMF but was never reviewed and has no Phase one study in this country.

From the above, it is obvious that a Pharmaceutical Company will not invest in a drug if they have no patent protection.

Metronidazole (Flagyl), Allopurinol (Zyloprim), Furoxone, Yodoxin, Diodoquin, Rifampicin, POTABA, Copper Sulfate, Bile Salts, are ALL generic drugs of which the patent (17 years) have long expired and which can be sold by any reliable drug manufacturer who meets the standard requirements of Drug Manufacturing Practices issued by the FDA. These compounds have valid NDA's which specifically list the INDICATIONS for which they were approved.

Any indication other than approved requires a complete NEW NDA, which we know will cost about \$2-3,000,000. Once the NDA is approved and the patent expired, one may obtain an ANDA (Abbreviated New Drug Application) and can market the compound within six months! Hence, the original NDA will NOT protect the manufacturer after the drug patent expired!

I have tried for several years to get the support of pharmaceutical companies to pay for the IND studies of their patented compounds. They had no interest because they did not believe that the compound would be effective for the treatment of rheumatoid arthritis.

Selection of Clotrimazole continued

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I finally obtained the support of Miles Pharmaceutical Company (Bayer AG) after several requests and personal meetings to evaluate Clotrimazole at a dose of 20mg/Kg per day for two days during six weeks. Pfizer and Ortho who have the patent for Tinidazole (Fasigyn) and Hoffman La Roche for (Ornidazole-Tiberal) refused to cooperate. Searle, the makers of Metronidazole (Flagyl) indicated that the patent expired and the drug is available to all manufacturers and therefore is not interested.

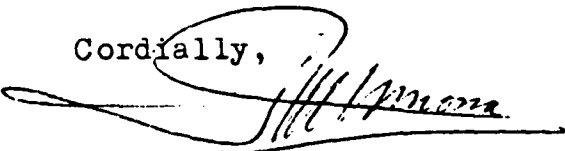
It is true that physicians may prescribe approved drugs for unapproved indications (Flagyl and Allopurinol for RA) but he should bear in mind that he assumes complete responsibility for any side-effect when treating a condition for which the drug has not been approved. This means that in case of a malpractice suit he cannot refer to the FDA's approval for protection.

I cannot guarantee that the proposed double-blind study with Clotrimazole will be successful and that we will confirm Wyburn-Mason's findings. But based on the successful treatment of several thousand patients suffering from active rheumatoid arthritis with anti-protozoal compounds by physicians all over the world during the last seven years and the "in vitro" reports of Clotrimazole against Acanthamoebae of two species, the Castellani and Culbertsoni reported by TONY CHAPDELAIN and our own findings against Naegleria Fowleri in concentrations of below one microgram/ml, we believe that Clotrimazole will be effective.

As requested by our Boardmembers at the Atlanta meeting of July 14, 1984 after suggested by Perry Chapdelaine, we have obtained the cooperation of Dr. Bradley Wells who will review the protocol and provide his expertise as a statistician before and after the study is completed. There will be a delay of one month because Dr. Wells will submit his report within two weeks and Dr. Turner will then revise the protocol (and budget) by August 20, 1984. The documents can then be submitted to the review board of Bowman Gray which meets at the end of every month. The IND can then be submitted by August 31st. and the study can start on October 1st., 1984 instead of September 1st. as originally planned.

We will keep you informed of any progress.

Cordially,



John R.A. Simoons, Ph.D.
President